HIMA
HEALTH INDUSTRY MANUFACTURERS ASSOCIATION

December 7, 1999

Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
Room 1061 (HFA-305)
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. 99D-2726; Draft Guidance on Labeling for Laboratory Tests

Dear Sir or Madam:

These comments are submitted by the Health Industry Manufacturers Association (HIMA) in response to the Food and Drug Administration's (FDA's) draft document titled "Guidance for Labeling for Laboratory Tests". HIMA is a Washington D.C. based trade association and the largest medical technology association in the world. HIMA represents more than 800 manufacturers of medical devices, diagnostic products, and medical information systems. HIMA's members manufacture more than 90 percent of the $58 billion of health care technology products purchased annually in the United States, and more than 50 percent of the 137 billion purchased annually in the world.

HIMA appreciates the opportunity to comment on this document. Our specific comments have been provided in the attached table. Our general comments are the following:

- The guidance document purports to establish new requirements for in vitro diagnostic (IVD) product labeling but the need for these new requirements has not been established. For new requirements, it is essential to establish the need for the requirements and to provide an explanation for their proposed intended use.

- The guidance document appears to undermine the concept of substantial equivalence by requiring that new tests be compared to the clinical status or condition of individuals/patients rather than to a predicate device. In essence such a requirement would create a PMA-like class of 510(k) products. If FDA intends to eliminate the concept of substantial equivalence, it should be done by regulation rather than by guidance.

- It appears that FDA is attempting to make some labeling distinction between products via a product to predicate comparison and those products that are cleared by a comparison to a

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- clinical condition or disease state. Such a distinction is not important to our customers. Most laboratorians are primarily interested in how a new test compares with what they are currently using. Delineating the distinctions in the product labeling will create an additional category of devices not sanctioned by Congress.

- The guidance document introduces new terminology that will be confusing to the laboratory user and be of questionable benefit. The proposed terminology is not consistent with other published information i.e., the labeling regulations (21 CFR 809.10), Workshop Manual FDA92-4165 or documents such as NCCLS GP10A.

- The document assumes that the package insert needs to include new types of information in order for physicians to understand the test. HIMA disagrees with this concept. For example, most physicians do not understand ROC curves and reviewing them would not benefit their practice. If the agency is recommending them as useful information, the agency should be prepared to educate the primary and secondary recipients of the diagnostic information about their use. Moreover, where it has been determined that specific physician information is necessary, as in some tests approved through the PMA process, a separate physician's brochure usually is prepared.

We also note that FDA, contrary to its "Good Guidance Practices" policy, is applying this guidance document in its review of current and pending 510(k) submissions. We assume that FDA would not like to leave the impression that it intends to adopt this guidance in spite of comments received from the public. We ask that FDA review and carefully consider the comments received during this public airing of the document before it applies the guidance document to product submissions.

In conclusion, HIMA believes this proposal intended to address a problem that has not been articulated in the document. We recommend that this draft guidance be withdrawn until DCLD clearly defines the problem FDA is attempting to address, document the determination that this effort should be a guidance rather than a regulation, and invite all stakeholders to participate in a discussion of any proposal to change the basis for product clearance.

Respectfully Submitted,

Carolyn D. Jones

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Specific Comments
on
FDA's Draft Guidance on Labeling for Laboratory Tests

SECTION	TEXT	COMMENT
Introduction Page 2 ¶ 1	"The evaluation of laboratory test performance should compare a new product's test results to some appropriate and relevant diagnostic benchmark that can be used to correlate results from the new test with the clinical status or condition of individuals/patients for whom the test is intended to be used."	There is already a benchmark process to evaluate new laboratory tests. New Class I and II IVD tests must show substantial equivalence to a predicate test. The PMA process requires a new Class III IVD test to be compared to a clinical status or condition in order to demonstrate clinical utility. Therefore, the benchmark for a 510(k) is a previously cleared or pre-amendment device. The benchmark for a PMA is a clinical status or condition. The purpose of the guidance and the issues intended to be resolved are unclear. The new Draft Guidance would have the labeling include information that directly correlates laboratory results to the clinical state of the patient. This type of detail is not appropriate for most IVD tests. The majority of IVD tests provide numeric measurements of specific analytes at a given point in time. The physician takes into account all relevant clinical information and then determines what these results mean with respect to the specific condition of the patient. While IVD test results may be closely correlated with the clinical status or condition, they are seldom used alone.
Introduction Page 2 ¶ 1	"The evaluation of laboratory test performance should compare a new product's test results . . ."	The guidance makes reference to a "new" test, and states that there are two major categories used to define the performance. FDA should define the term new. A truly "new" test would be one for which there is no predicate for comparison and for which "Operational Truth" would be an appropriate indicator for diagnostic performance.

SECTION	TEXT	COMMENT
Introduction Page 2 ¶ 1	"Determination of the clinical status of patients whose specimens are used in an evaluation may be based on laboratory and/or clinical endpoints."	The author does not define "laboratory and/or clinical end-points". If it refers to "reference intervals" and "cut off values," there is not a one-to-one correlation between reference intervals and cut-off values and disease states. Clinical and laboratory results are not the sole determinant of diagnoses. If the author means "clinical endpoints" equals "outcomes," laboratory results alone cannot be relied upon as the sole basis for evaluating the efficacy of IVD tests. A physician considers a wide variety of clinical data, including x-rays, physical exams, laboratory data, and personal experience in determining a final diagnosis. A diagnosis is not based solely on laboratory data.
Introduction Page 2 ¶ 1	" . . ., the Division of Clinical Laboratory Devices recognizes two major categories of endpoints for assessing diagnostic performance of new "in vitro diagnostic" assays . . .(1)Operational Truth or (2) Laboratory Equivalence."	This guidance superimposes two distinct classes of 510(k) products over the existing medical device classes. Products cleared via comparison to a clinical study and those cleared via a head-to-head comparison to a predicate device. Such an approach will create the impression that products cleared via a comparison to a predicate device are somehow inferior to other products.
Introduction Page 2 ¶ 1	"Characterization of test performance is important to allow labeling that will clarify the performance of the device for both laboratories and health care givers."	The meaning of this sentence is unclear. Labeling that is in compliance with 21 CFR 809.10 (a) & (b) has articulated the performance of IVD tests to the general satisfaction of the user community for over 20 years.
Operational Truth Page 2 Item 1	"Test performance is characterized in terms of direct comparison to the relevant clinical condition or status of individuals/patients evaluated."	The concept of "Operational Truth" would mean that manufacturers would have to prove specificity not by comparison to a "reference" method but by using other objective disease criteria. We do not believe that this can be done practically for an assay intended for screening of individuals such as in a donor environment. Presumably, one would have to test all positive and negative samples by methods that "prove" the disease state. In some cases, existing "confirmatory assays" are not designed for testing these populations and in other cases it is not economically feasible. In these instances, rather than having to prove disease state an assumption of zero percent prevalence should be used as the criteria. On the other hand, proving clinical sensitivity using operational truth is possible to some extent. Where it is not practical or feasible, an assumption of 100% prevalence of the analyte in the patient population could be used as the criteria, as long as this is indicated in the product labeling.

SECTION	TEXT	COMMENT
Operational Truth Page 2 Item 1	"The case definitions being used as the reference point in determining performance should be clearly referenced and explained either in performance tables and/or supporting text. "	This section proposes to have labeling include information established from autopsy, outcome studies, diagnostic algorithms or other methods, and compared to established case definitions. While the PMAs for some Class III IVD products require studies as described in this section of the Draft Guidance, including this amount of detail in a product insert is of limited value to the user. Case definitions are appropriate to include in a submission to the FDA to verify claims of safety and efficacy. These requirements are more appropriate to a PMA Guidance Document, not a Labeling Guidance Document. Users need information that is succinct and in summary form. Compliance with 21 CFR 809.10 (a) & (b) provides the appropriate amount of detail. Manufacturers often provide supplemental information in a Physician's Brochure and/or a Technical Bulletin.
Laboratory Equivalence Page 2 Item 2	"Performance of a new test is characterized in terms of comparison to a predicate."	The boldface "**Laboratory Equivalence**" title of this paragraph should be changed to "**Substantial Equivalence**". The majority of IVDs are brought to market via a determination of substantial equivalence. Laboratory equivalence introduces a new term that has no statutory or regulatory meaning.
Proposed Labeling Page 3 ¶ 1	"All package inserts for laboratory tests should clearly explain how performance has been deduced or determined."	As noted above, labeling that is compliant with 21 CFR 809.10 (a) & (b) has articulated the performance of IVD tests to the general satisfaction of the user community for over 20 years.
Proposed Labeling Page 3 ¶ 1 Bullet 1	"Estimates of sensitivity, specificity, and ROC (Receiver Operating Characteristic) Curves along with confidence intervals are appropriate measures of performance and may be presented in labeling."	While ROC analysis is a useful tool for determining clinical sensitivity and clinical specificity, very few laboratories and even fewer health care providers understand ROC curves as a measure of performance. A ROC analysis will have no meaning in the majority of clinical situations. This sentence should be edited to" Estimates of clinical sensitivity, clinical specificity..." to avoid ambiguity.

Proposed Labeling Page 3 ¶ 1 Bullets 3 and 4	"If specimens have been preselected for testing . . . sensitivity and specificity claims may still be appropriate . . . The effects of prevalence on the usefulness and reliability of the test should be discussed . . . with performance estimates translated into the hypothetical predictive values for documented frequency of the condition/disease . . ."	The guidance should require a discussion of prevalence and predictive values whenever a sensitivity and specificity claim is made. Simply knowing specificity and sensitivity without knowing the prevalence of the test population versus the true clinical population seen by that practitioner is misleading.
Proposed Labeling Page 3 ¶ 2 Bullet 1	"A test that has been characterized to a predicate but has not been compared to "true" diagnostic states should be labeled WITHOUT sensitivity or specificity claims."	Rather than requiring that a test be labeled without sensitivity and specificity claims, FDA should make a distinction between analytical sensitivity and specificity and clinical sensitivity and specificity. It is customary to provide sensitivity of an assay based on the level of the specific analyte that can be detected. If we state our claims in terms of agreement, what is the point of doing confirmatory testing or discordant resolution? It will show truth for discordants and positives but will say nothing about truth where both results are negative. In order to remain consistent with 21 CFR 809.10 (b) (12) and to avoid ambiguity this sentence should be edited to read: "A test that has been characterized to a predicate but has not been compared to 'true' diagnostic states, should be labeled without clinical sensitivity or clinical specificity claims."
Proposed Labeling Page 3 ¶ 2 Bullet 1	"Relative performance may be described in terms of agreement, co-positivity and co-negativity, or using similar terms."	The FDA, in cooperation with NCCLS, CAP, or CDC, should conduct an educational campaign directed at the consumer on measures of performance of laboratory tests. While the guidance describes the correct scientific terminology to assess performance criteria for some IVD's, consumers will not be comfortable with co-positivity, co-negativity or ROC curves in describing performance characteristics. A standard glossary of terms accepted by the entire medical community is needed. Due to global regulatory requirements for labeling, manufacturers do not have label space to add a glossary or explain the use of these terms. If these terms are utilized and not understood, the labeling may become misleading.